

## REMARKS

Claims 1-5, 8-11 and 14-16 are pending in this application. Applicants appreciate the Examiner's withdrawal of rejections under 35 U.S.C. §§ 102 and 112. For reasons discussed below, the rejection under 35 U.S.C. § 103 should also be withdrawn.

On pages 2-8 of the Office Action, the rejection of claims 1-5, 8-11 and 14-16 under 35 U.S.C. § 103 is maintained as being allegedly obvious over U.S. Patent No. 5,994,069 to Hall *et al.* ("Hall") in view of U.S. Patent No. 6,387,621 to Wittwer *et al.* ("Wittwer"). Applicants respectfully traverse this rejection.

The Patent Office bears the burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. *In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995); *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). To establish a *prima facie* case of obviousness, the Patent Office must first show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, it must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the Patent Office must show that the prior art teaches or suggests all the claim limitations. *Manual of Patent Examining Procedure*, § 2143; *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). These criteria must be satisfied with factual and objective evidence found in the prior art: an examiner's conclusory statement cannot form a basis for a *prima facie* case of obviousness. *In re Sang-Su Lee*, 277 F.3d 1338, 1343-4 (Fed. Cir. 2002). Applicants respectfully submit that these criteria are not met by the combination of Hall and Wittwer.

As the Examiner correctly recognized, Hall does not teach modes of data analysis to overcome the problem of undesired background noise. Office Action, page 5. Wittwer does not cure this deficiency. Wittwer is directed to the analysis of a sample for the presence of a nucleic acid wherein the sample is amplified using PCR, in the presence of a fluorescence probe. Wittwer, Abstract. In order to achieve that, "[a] baseline region is determined by comparing the fluorescence at various amplification cycles, and the fluorescence at a selected amplification cycle is compared to the baseline region." *Id.* (emphasis added). Therefore, Wittwer does not provide a means of overcoming background

noise, but instead compensates for it. Wittwer, col. 2, lines 24-26 (“Without compensation for baseline drift, automated amplification data analysis can easily provide both false negative and false positive results.”). In contrast, the claimed invention does not require the determination of a baseline region or the compensation for baseline drift.

Referring to Figure 5 of Wittwer, the Examiner contends that linear behavior of negative signals and non-linear behavior of positive signals are disclosed in Wittwer. Office Action, page 5. In addition, the Examiner refers to col. 7, lines 5-45 of Wittwer as allegedly providing the analytical frame work for non-linear, quadratic behavior of positive results shown in Figure 5 of Wittwer. *Id.* Applicants respectfully disagree with each of these allegations.

First, Figure 5 does not show that negative signals exhibit linear behavior: the negative result shown in Figure 5 appears to be a curve obtained from second order kinetics. Even assuming, however, that the negative result depicted in Figure 5 does represent linear behavior, those of ordinary skill in the art, looking at Figure 5, would not have understood that negative results are always linear and positive results are always non-linear. This is because Figure 5 is a mere representation of how to determine a background region, *i.e.*, by selecting a sliding window with a slope of lowest absolute value (closest to zero). Wittwer, col. 6, line 55 - col. 7, line 4. In other words, Figure 5 contemplates that the data points selected in the confidence band, when interpolated, have a slope close to zero, but not that negative results are represented in a linear line and positive results in a non-linear curve. As such, those of ordinary skill in the art would have learned nothing from Figure 5 that would suggest the claimed invention.

In addition, contrary to the Examiner’s allegation, the description in col. 7, lines 5-45 of Wittwer does not provide an analytical framework for non-linear, quadratic behavior of positive signals disclosed in its Figure 5. Rather, the description therein provides methods of determining the baseline wherein the lowest slope appears at obviously unusual time points:

This algorithm should work well in most cases. However, with the high copy fluorescence curve type (Fig. 3D), the shallowest slope might be found at early cycles (resulting in a[n] [in]correct [sic] positive call) or at late cycles (resulting in an incorrect negative call). This exception may be handled by analyzing the curve shape.

Wittwer, col. 7, lines 5-10. Wittwer goes on to describe that first and second derivatives are obtained using the sliding window analysis, and where the curve shape is well behaved, *i.e.*,

shows S-type behavior, then “the background is only selected from sliding windows centered at cycle numbers less than the second derivative maximum.” *Id.* at col. 7, lines 19-29.

In other words, Wittwer discloses the examination of the curve shape with regard to how best to determine the background window. Wittwer, however, does not teach or suggest obtaining a data set  $(t, S(t))$  by detecting the reporter at a plurality of times, transforming it to provide  $(t^*, S^*(t^*))$ , and determining whether the transformed data set exhibits non-linear behavior. Moreover, Wittwer does not teach or suggest that the target nucleotide is detected if the transformed data set exhibits non-linear behavior.

In sum, the methods disclosed in Wittwer concern how to obtain a stable baseline with a confidence band, and comparing a signal generated from a specific sample at specific time point with the determined confidence band. If the signal is outside the confidence interval, the sample is positive. Wittwer, col. 8, lines 63-67. However, Wittwer does not disclose or suggest fitting the signal to a non-linear function in order to determine whether the signal is positive. Therefore, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. § 103 should be withdrawn.

Additional reasons exist as to why this rejection should be withdrawn. In response to Applicants’ argument that no suggestion or motivation to combine Hall and Wittwer was present, the Examiner states that significant motivation existed because Hall recognized that background is a problem in its methods, and Wittwer stated that its analysis method is applicable to other amplification systems. Applicants respectfully disagree.

As described in the specification of this application, the background signal typically obtained during an invasion assay is generated by the binding of the primary invader oligonucleotide, which is intended to bind only to the template DNA, to some degree to the secondary structure, causing cleavage of that structure. Specification, page 2, lines 13-18. In other words, the background signal generated during an invasion assay is specific to that type of DNA amplification. The portions of Hall referred to by the Examiner are in accord with this. Hall discloses that background cleavage due to thermal breakdown of probe occurs “when oligonucleotide probes are used in cleavage detection assays at elevated temperature.” Hall, col. 54, lines 21-26 (emphasis added). Therefore, those of ordinary skill in the art would not have been motivated to use Wittwer’s methods, which were disclosed in connection with the background fluorescence in conventional PCR, to overcome the background problems specific to an invasion assay.


Moreover, a close reading of Wittwer reveals that Wittwer, when it states that “these algorithms may be applied to any amplification system,” is not referring to other

amplification methods, but is instead referring to other PCR platforms. Hall states that “[w]hile these algorithms may be applied to any amplification system, it is preferred to integrate these algorithms into the LightCycler™ platform.” Hall, col. 5, lines 46-49. As such, it is evident that Hall’s reference to “any amplification system” does not concern other amplification methods. Thus, Applicants respectfully submit that the rejection of the claims under 35 U.S.C. § 103 should be withdrawn for numerous reasons.

No fee is believed due for this response. However, if a fee is due, please charge such fee to Jones Day Deposit Account No. 503013. A copy of this sheet is enclosed.

Respectfully submitted,

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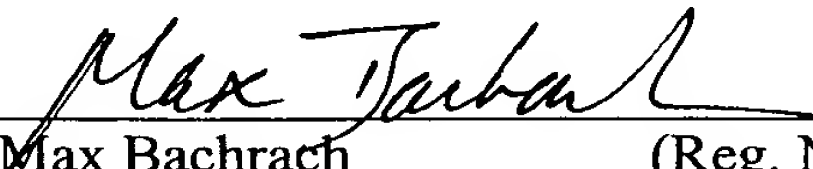
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